



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB99/01474 <b>(22) International Filing Date:</b> 11 May 1999 (11.05.99) <b>(30) Priority Data:</b> 9810886.3 13 May 1998 (13.05.98) GB <b>(71) Applicant (for all designated States except US):</b> ELI LILLY AND COMPANY LIMITED [GB/GB]; Kingsclere Road, Basingstoke, Hampshire RG21 6XA (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> FAIRHURST, John [GB/GB]; 17 Hinton Fields, Kings Worthy, Winchester, Hampshire SO23 7QB (GB). GALLAGHER, Peter, Thaddeus [GB/GB]; 27 Ryves Avenue, Yateley, Hampshire GU46 6FB (GB). MILES, Martin, Victor [GB/GB]; 21 Wensleydale Gardens, Hampton, Middlesex TW12 2LU (GB). OWTON, William, Martin [GB/GB]; 29 Ridgeway Close, Lightwater, Surrey GU18 5XX (GB). SMITH, Colin, William [GB/GB]; 36 Avebury, Bracknell, Berkshire RG12 4SQ (GB). <b>(74) Agent:</b> HUDSON, Christopher, Mark; Eli Lilly and Company Limited, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH (GB).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> INDOLE DERIVATIVES AS 5-HT <sub>2A</sub> LIGANDS AND AS SEROTONINE REUPTAKE INHIBITORS  <div style="text-align: center;"> </div> <p style="text-align: right;">(I)</p>		
<b>(57) Abstract</b>  <p>Pharmaceutical compounds of formula (I) in which n is 1 to 6, m is 1 or 2 and p is 1 or 2, R<sup>1</sup> and R<sup>2</sup> are each hydrogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, HO-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkythio, halo, optionally substituted phenyl, optionally substituted phenyl-C<sub>1-4</sub> alkyl, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are attached form a C<sub>3-6</sub> cycloalkyl group, &gt;C=O, C=NOR' where R' is hydrogen or C<sub>1-4</sub> alkyl, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are each hydrogen, halo, nitro, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl-CO-, where m is 0, 1 or 2, R'R''N-SO<sub>2</sub>-, -COOR', -CONR'R'', -NR'R''-N(OR')COOR'', -COR', -NHSO<sub>2</sub>R', where R' and R'' are each hydrogen or C<sub>1-4</sub> alkyl, R<sup>6</sup> and R<sup>7</sup> are each hydrogen or C<sub>1-4</sub> alkyl, X is oxygen or sulphur, the dotted line represents an optional double bond, and the fluorine atom is attached at the 6- or 7-position; and salts thereof.</p>		

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INDOLE DERIVATIVES AS 5-HT<sub>2A</sub> LIGANDS AND AS SEROTONINE REUPTAKE INHIBITORS

This invention relates to pharmaceutical compounds,  
their preparation and use.

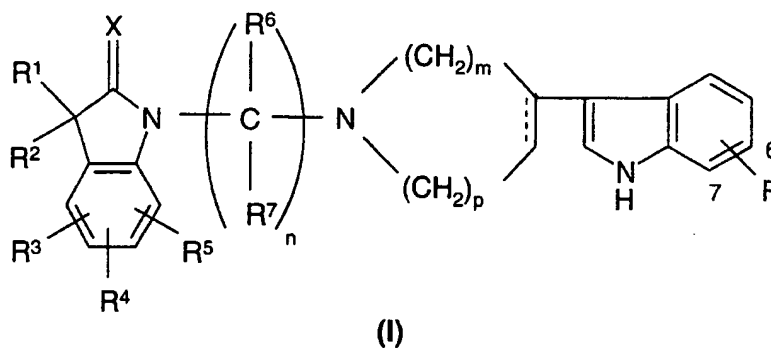
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Compounds of the indole-2-one type have been described  
in the literature as having potential use as analgesics  
or for treating cognitive disorders or as cholinesterase  
inhibitors as, for example, in J. Med. Chem. 1991, 34,  
10 827-841, WO 93/12085 and CA 119: 225964t.

EP-A 0 780 388 discloses certain indole-2-one compounds  
with central nervous system properties.

The compounds of the invention are of the following

15 formula:



in which n is 1 to 6, m is 1 or 2 and p is 1 or 2,

20

R<sup>1</sup> and R<sup>2</sup> are each hydrogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, HO-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkylthio, halo, optionally substituted phenyl, optionally substituted phenyl-C<sub>1-4</sub> alkyl, or R<sup>1</sup> and R<sup>2</sup> together  
5 with the carbon atom to which they are attached form a C<sub>3-6</sub> cycloalkyl group, >C=O, >C=NOR' where R' is hydrogen or C<sub>1-4</sub> alkyl,

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are each hydrogen, halo, nitro, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl-CO-, where m is 0, 1 or  
10 2, R'R''N-SO<sub>2</sub>-, -COOR', -CONR'R'', -NR'R'', -N(OR')COOR'', -COR', -NHSO<sub>2</sub>R', where R' and R'' are each hydrogen or C<sub>1-4</sub> alkyl,

15 R<sup>6</sup> and R<sup>7</sup> are each hydrogen or C<sub>1-4</sub> alkyl,

X is oxygen or sulphur,

the dotted line represents an optional double bond, and  
20

the fluorine atom is attached at the 6- or 7-position;

and salts thereof.

25 The compounds of the invention and their pharmaceutically acceptable salts are indicated for use

in the treatment of disorders of the central nervous system. They are active in tests that indicate serotonergic modulation.

5 In the above formula (I), a C<sub>1-4</sub> alkyl group includes methyl, ethyl, propyl, isopropyl, butyl and tert. butyl, and is preferably methyl or ethyl. A C<sub>1-4</sub> alkoxy group is one such alkyl group linked to a ring via an oxygen atom, and a halo atom is preferably chlorine, bromine or  
10 fluorine, and especially chlorine or fluorine. A substituted phenyl group is phenyl substituted with one or more, for example one to three, substituents selected from, for example, C<sub>1-4</sub> alkyl, especially methyl, C<sub>1-4</sub> alkoxy, especially methoxy and ethoxy, hydroxy, nitro,  
15 cyano, halo, especially chloro or fluoro, trihalomethyl, especially trifluoromethyl, carboxy and C<sub>1-4</sub> alkoxy-carbonyl. An optionally substituted phenyl-C<sub>1-4</sub> alkyl group is an optionally substituted phenyl attached through a C<sub>1-4</sub> alkyl group, and is preferably optionally  
20 substituted phenyl-(CH<sub>2</sub>)<sub>x</sub>- where x is 1 or 2, and most preferably optionally substituted benzyl.

It will be appreciated that when n is more than one, the recurring unit is not necessarily the same.

25

Preferred compounds are those which exhibit one or more of the following features:

- 5 (i) the fluorine substituent is in the 6-position
- (ii) x is oxygen
- (iii) the dotted line represents a double bond
- 10 (iv) m is 2 and p is 1
- (v)  $R^1$  and  $R^2$  are each hydrogen,  $C_{1-4}$  alkyl or  $C_{1-4}$  alkylthio
- 15 (vi)  $R^1$  and  $R^2$  are both  $C_{1-4}$  alkyl or benzyl
- (vii) n is 2
- (viii)  $R^6$  and  $R^7$  are hydrogen
- 20 (ix)  $R^3$ ,  $R^4$  and  $R^5$  are each hydrogen.

As indicated above, it is, of course, possible to prepare salts of the compound of the invention and such

25 salts are included in the invention. Acid addition

salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or  
5 with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric, salicyclic, o-acetoxybenzoic, or organic sulphonic, 2-hydroxyethane sulphonic, toluene-p-sulphonic, or naphthalene-2-sulphonic acid.

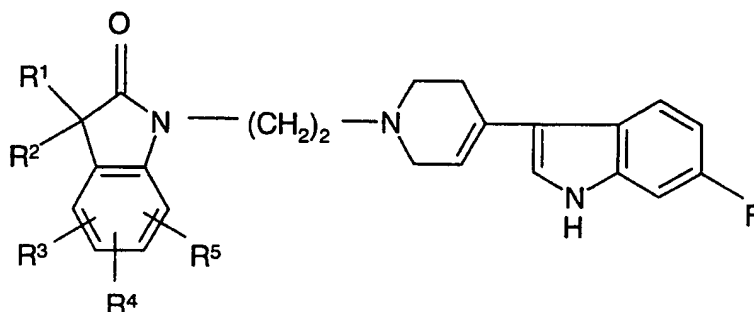
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In addition to the pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example  
15 pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

Some of the compounds of the invention contain one or  
20 more asymmetric carbon atoms which gives rise to isomers. These compounds are normally prepared as racemic mixtures and can conveniently be used as such, but individual isomers can be isolated by conventional techniques, if so desired. Such racemic mixtures and  
25 individual optical isomers form part of the present

invention. It is preferred to use an enantiomerically pure form.

A preferred group of compounds according to the  
5 invention is of formula:

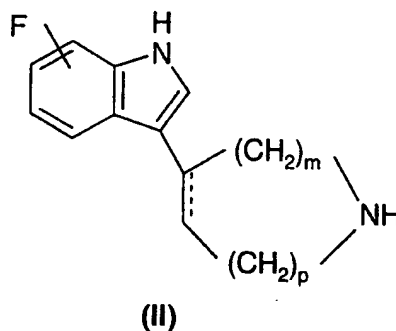


in which  $R^1$  and  $R^2$  are each hydrogen or  $C_{1-4}$  alkyl, and  
 $R^3$ ,  $R^4$  and  $R^5$  are each hydrogen;

10

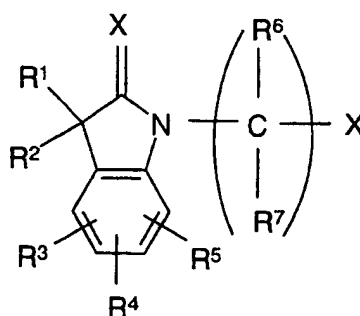
and salts thereof.

The invention also includes a process for producing a  
compound of formula (I) above, which comprises reacting  
15 a compound of the formula:





with a compound of the formula:



(III)

5

where the substituents have the values given above, and X is a leaving group such as, for example, a halo atom, or a mesylate or tosylate. The coupling can also be effected by reacting the compound of formula (II) with an aldehyde equivalent of the compound of formula (III). Such aldehydes can be prepared from the appropriate terminal alkene by oxidation followed by reductive amination using sodium cyanoborohydride with the compound of formula (II).

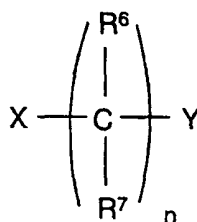
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The reaction is preferably carried out in a polar solvent such as, for example, acetonitrile or water, at a temperature of from 50° C. to 150° C., and in the presence of sodium iodide and a base such as, for example, sodium carbonate.

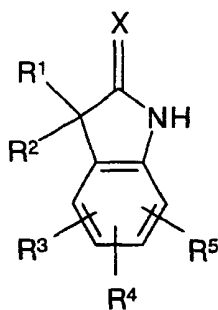
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The intermediate compounds of formula (II) and  
formula (III) are known in the art. Compounds of  
formula (III) can be prepared by reacting the  
5 appropriate alkane derivative of formula:



(IV)

where X is a leaving group and Y is halo, preferably  
10 bromo, with a compound of formula:



(V)

As mentioned above, the compounds of the invention and  
15 their pharmaceutically acceptable salts have useful

central nervous system activity. The compounds are active at the serotonin, 5-HT<sub>2A</sub>, receptor. Their binding activity has been demonstrated in a test described by Leysen, J. E. et al., Molecular Pharmacology Vol. 21, 1981, pages 301-314, in which the affinity of the compound for the 2A receptor is measured by its ability to displace the ligand [<sup>3</sup>H] ketanserine. The compounds are also an active serotonin reuptake inhibitor as measured by its displacement of [<sup>3</sup>H] paroxetine at the reuptake site, Neuropharmacology Vol. 32 No. 8, 1993, pages 737-743.

Because of their selective affinity for 5-HT receptors, the compounds of the present invention are indicated for use in treating a variety of conditions such as depression, obesity, bulimia, alcoholism, pain, hypertension, ageing, memory loss, sexual dysfunction, anxiety, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis, Alzheimer's and sleep disorders.

The compounds of the invention are effective over a wide dosage range, the actual dose administered being dependent on such factors as the particular compound being used, the condition being treated and the type and size of mammal being treated. However, the dosage

required will normally fall within the range of 0.01 to 20 mg/kg per day, for example in the treatment of adult humans, dosages of from 0.5 to 100 mg per day may be used.

5

The compounds of the invention will normally be administered orally or by injection and, for this purpose, the compounds will usually be utilised in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

Accordingly the invention includes a pharmaceutical composition comprising as active ingredient a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof, associated with a pharmaceutically acceptable excipient. In making the compositions of the invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. The excipient may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Some examples of suitable excipients are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum

acacia, calcium phosphate, alginates, tragacanth,  
gelatin syrup, methyl cellulose, methyl- and propyl-  
hydroxybenzoate, talc, magnesium stearate or oil. The  
compositions of the invention may, if desired, be  
5 formulated so as to provide quick, sustained or delayed  
release of the active ingredient after administration to  
the patient.

Depending on the route of administration, the foregoing  
10 compositions may be formulated as tablets, capsules or  
suspensions for oral use and injection solutions or  
suspensions for parenteral use or as suppositories.  
Preferably the compositions are formulated in a dosage  
unit form, each dosage containing from 0.5 to 100 mg,  
15 more usually 1 to 100 mg, of the active ingredient.

The following Preparations and Examples illustrate  
methods of making compounds of the invention.

PREPARATIONS

- (1) N-Acetyl-1,3-dihydro-2H-indol-2-one: 1,3-Dihydro-2H-indol-2-one (35.6g, 0.268mol) suspended in acetic anhydride (30mls) and mixture refluxed for 20 hours. Filtered and washed with diethyl ether (50mls) dried in vacuo at 80degC to give a solid.
- 3-Spiro-1'-cyclopropyl-1,3-dihydro-2H-indol-2-one: N-Acetyl-1,3-dihydro-2H-indol-2-one (15.0g, 85.7mmols) dissolved in dimethylformamide (180mls) and added to suspension of sodium hydride (60% in oil dispersion, 7.2g, 4.32g, 0.18mol) in dimethylformamide (30mls). After 30 minutes 1,2-dibromoethane (17.71g, 94.27mmols) was added and the mixture stirred at ambient temperature for 20 hours. More sodium hydride (1.4g, 0.84g, 14mmol) was added followed by 1,2-dibromoethane (4g, 21.96mmol) and stirred for 1h at ambient temperature. The solvent was removed in vacuo and the residue treated with water (100mls) added extracted with ethyl acetate (2x150mls), separated and dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to give an oil which was purified by column chromatography on silica eluting with ethyl acetate/hexane to give 3-spiro-1'-cyclopropyl-1,3-dihydro-2H-indol-2-one as an oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ 1.54 (2H m), 1.78 (2H m), 6.82 (1H d), 7.02 (2H m), 7.22 (1H m), 9.0 (1H broad)

5 (2) Cyclobutylphenylhydrazide : Phenylhydrazine (9.21g, 85.2mmols) was added to an ice bath cooled mixture of cyclobutane carbonyl chloride (10.1g , 85.2mmols) and triethylamine (8.62g, 85.2mmols) dissolved in dichloromethane (100mls) allowed to  
10 warm to ambient temperature and stirred for 48h. The organic layer was washed with water, separated. dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo. The resultant solid was washed with diethyl ether (10mls) and dried under suction to give a solid.

15

3-Spiro-1'-cyclobutyl-1,3-dihydro-2H-indol-2-one:  
Cyclobutylphenylhydrazide (7.14g, 37.6mmols) combined with calcium hydride(2.37g) and heated to 240degC for 30 mins., cooled and methanol(40mls)  
20 and water (10mls) added followed by hydrochloric acid ( $d=1.16\text{g/ml}$ , 30mls) the resultant mixture heated under reflux for 1h., then basified with 5M sodium hydroxide to pH11 and the mixture extracted with diethyl ether. The ether layer was separated  
25 and dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo to give an oil which was chromatographed on silica eluting with ethyl acetate/hexane silica to

give 3-spiro-1'-cyclobutyl-1,3-dihydro-2H-indol-2-one as an oil.

(3) 3-Spiro-1'-cyclopentyl-1,3-dihydro-2H-indol-2-one -

5 N-acetyl oxindole (5.0g, 28.6mmols) was dissolved in tetrahydrofuran (100mls) under nitrogen, cooled to -78C and 2.0M lithium diisopropylamide in THF (15.45ml, 30.9mmol) added and left to stir for 30mins. 1,4-dibromobutane (6.48g, 30mmols) added  
10 and mixture left for 1 hour at -78C. More lithium diisopropylamide in THF (15.45ml, 30.9mmol) added and the mixture left to warm to ambient temperature. The solvent was removed in vacuo and water (100mls) added, the aqueous extracted with  
15 ethyl acetate (2x150ml). The aqueous layer was separated, the organic layer dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. The residue was purified by column chromatography on silica with ethyl acetate / hexane to give 3-spiro-1'-  
20 cyclopentyl-1,3-dihydro-2H-indol-2-one as an oil.

(4) Cyclohex-3,4-enylphenylhydrazide

A mixture of cyclohex-3-ene-1-carboxylic acid (15.23g, 0.120mols), and phenylhydrazine (13.16g ,  
25 0.122mols) dissolved in toluene (100mls) and heated under reflux for 18h with water separation using a Dean Stark apparatus. The toluene evaporated in



vacuo and the residue recrystallised from diethyl ether to give a solid.

3-Spiro-1'-cyclohexyl-1,3-dihydro-2H-indol-2-one

5 To a -78C solution of 1,3-dihydro-2H-indol-2-one (10g, 75.1mmols) dissolved in tetrahydrofuran (200mls) was added lithium bis(trimethylsilylamide) (1.0M in THF, 375mls, 0.375mol) was added keeping the temperature below -  
10 40C. The mixture was allowed to stir for 150 minutes at -40C cooled to -78C and 1,5-dibromopentane (86.35g 0.375mols) added. The reaction mixture was allowed to warm to ambient temperature and stirred for 3 hours then heated  
15 under reflux for 7 hours, concentrated in vacuo, dissolved in ethyl acetate (200mls) and washed with saturated aqueous ammonium chloride (100mls), dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. The resultant solid was purified by chromatography  
20 (silica / ethyl acetate / hexane) to give 3-spiro-1'-cyclohexyl-1,3-dihydro-2H-indol-2-one as a solid.

(5) Methyl 2-nitrophenylacetate

25 A mixture of 2-nitrophenylacetic acid (300g, 1.66mol) and sulfuric acid (d =1.84g/ml, 6ml) in methanol (6l) was heated under reflux for 21h. The

solvent was removed in vacuo and the residue dissolved in dichloromethane (2l). The dichloromethane solution was then washed with saturated aqueous sodium carbonate solution (600ml), brine (500ml), dried (MgSO<sub>4</sub>), filtered and then evaporated in vacuo.

Methyl 2-methyl-2-(2-nitrophenyl)propionate

Hexane (1000ml) was added to sodium hydride (60%, 180g, 4.5mol) and stirred under nitrogen for 5 minutes and then allowed to settle. The hexane was removed by decantation and replaced with dry dimethylformamide (3l). More sodium hydride (unwashed 14g, 0.35mol) was then added and the reaction mixture was cooled to 5C and treated with methyl 2-nitrophenylacetate (323g 1.66mol) in dry dimethylformamide (1500ml) during 27mins whilst the internal temperature was kept below 5C. The mixture was then allowed to stir for 2h allowing the temperature to rise to ambient. The purple reaction mixture was then cooled to 0C and a solution of iodomethane (367ml, 5.8mol) in dry dimethylformamide was added dropwise during 38mins at 0-5C and maintained at this temperature for 45mins then allowed to warm to ambient temperature and stirred for 22h. The reaction mixture was then poured onto ice (5kg) diluted with water (8000ml)

stirred for 10mins and then extracted with diethyl ether (3x1500ml), the organic extracts combined filtered through celite, dried (MgSO<sub>4</sub>), filtered and evaporated in vacuo to give an oil which was used without further purification.

3,3-Dimethyl-1,3-dihydro-2H-indol-2-one

To a well stirred mixture of iron powder (476g, 8.52mol) in acetic acid (3000ml) at 92C under nitrogen was added dropwise during 40mins a solution of methyl 2-methyl-2-(2-nitrophenyl)propionate (395g, 1.77mol) in acetic acid (500ml). The resultant exothermic reaction was maintained at 100C for 15 mins cooled to 30C, filtered and the filtered iron washed with acetic acid, combined with the reaction mixture and evaporated in vacuo to give a residue which was dissolved in ethyl acetate and then washed with hydrochloric acid (1000ml), brine (1000ml), dried (MgSO<sub>4</sub>) filtered and evaporated in vacuo to give a crystalline solid.

(6) 3-Methyl-3-methylthio-1,3-dihydro-2H-indol-2-one:

1,3-Dihydroindol-2(3H)-one (3.3g, 25mmol) and tetramethylethylenediamine (6.4g, 55mmol) was dissolved in freshly distilled tetrahydrofuran under nitrogen and cooled to -75°C. in an

acetone/dry ice bath. n-Butyllithium (2.5M, 22ml, 55mmol) was added and the mixture was stirred at -75°C. for 30 minutes. Iodomethane (3.57g, 25mmol) was added and the mixture was allowed to warm to -20°C., the mixture was recooled to -75°C. then dimethyl disulfide (2.35g, 25mmol) was added and the mixture was allowed to warm to room temperature. Water (5 ml) was added and the mixture was concentrated under reduced pressure to a yellow oil. Column chromatography on silica gel (eluent ethyl acetate/hexane) gave 3-methyl-3-methylthio-1,3-dihydro-2H-indol-2-one as a yellow oil which solidified on standing.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.61(3H s), 1.91(3H s), 6.96(1H d), 7.04(1H t), 7.12(2H m), 8.05 (1h broad).

(7) 5-Bromo-3,3-dimethyl-1,3-dihydro-2H-indol-2-one : 3,3-dimethyl-1,3-dihydro-2H-indol-2-one (1.12g, 6.95mmol) was dissolved in chloroform and stirred at room temperature under nitrogen. Bromine (1.12g) was added and the mixture was heated under reflux until HBr evolution ceased and the bromine colour was discharged from the solution. The solution was washed with sodium metabisulphite solution and sodium hydrogen carbonate solution, dried (MgSO<sub>4</sub>), filtered and concentrated to dry

under reduced pressure to give 5-bromo-3,3-dimethyl-1,3-dihydro-2H-indol-2-one as a yellow solid.

5         $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.39 (6H s), 6.8 (1H d), 7.3 (2H m), 7.9 (1H broad)

(8) 5,6-Difluoro-1,3-dihydro-2H-indol-2-one: 3,4-Difluoroacetonitrile (5g, 32.7mmol) was added dropwise to 90% fuming nitric acid (25ml) stirred and cooled in an ice/water bath. After 15 hours' stirring the mixture was poured into water, neutralised with sodium bicarbonate and extracted into dichloromethane. The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting oil was dissolved in boron trifluoride acetic acid complex (30ml), water (1 ml) was added and the mixture was heated under reflux for three hours. The mixture was poured into water, the pH was adjusted to pH4 and the mixture was extracted with ethyl acetate. The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting oily solid was dissolved in acetic acid, iron powder was added and the mixture was heated under reflux for 1 hour. The mixture was filtered through Celite and concentrated under reduced

pressure to a dark oil. Column chromatography on silica gel (eluent chloroform/methanol) gave 5,6-difluoro-1,3-dihydro-2H-indol-2-one as an orange solid.

5

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.48(2H s), 6.7(1H dd), 7.05(1H dd), 8.65(1H broad)

- (9) 3,3,4-Trimethyl-1,3-dihydro-2H-indol-2-one and  
10 3,3,6-Trimethyl-1,3-dihydro-2H-indol-2-one :  
Prepared from N-isobutyl-3-methylphenylhydrazide by the method of Endler and Becker; Organic Syntheses Coll. vol. 4 page 657 and separated by preparative HPLC.

15

Melting point 3,3,4-Trimethyl-1,3-dihydro-2H-indol-2-one  $-133^\circ \text{C}$ .

20

Melting point - 3,3,6-Trimethyl-1,3-Dihydro-2H-indol-2-one  $-178^\circ \text{C}$ .

- (10) 3,3-Dimethyl-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one : 3,3-Dimethyl-1,3-dihydro-2H-indol-2-one (6.3g, 40mmol) was dissolved in dry  
25 dimethylformamide under nitrogen at room temperature. Sodium hydride (60% dispersion in mineral oil, 1.8g, 45mmol) was added and the

mixture was stirred until gas evolution ceased.  
2-(2-Chloroethoxy)tetrahydro-2H-pyran (7.5g,  
42mmol) and sodium iodide (0.6g, 4mmol) was added  
and the mixture was warmed to 75° C. for 15 hours.  
5 Water was added and the mixture was concentrated  
under reduced pressure. The residue was taken up in  
ethyl acetate, washed (x 3) with water, dried  
(MgSO<sub>4</sub>), filtered and concentrated under reduced  
pressure. The resulting oil was taken up in  
10 methanol, para toluenesulphonic acid (0.75g, 4mmol)  
was added and the mixture was stirred at room  
temperature for 12 hours. The mixture was  
concentrated under reduced pressure, taken up in  
ethyl acetate, washed (x 3) with aqueous sodium  
15 hydrogen carbonate solution dried (MgSO<sub>4</sub>), filtered  
and concentrated under reduced pressure. The  
resulting oil was purified by chromatography on  
silica gel, eluent hexane/ethyl acetate, to give  
3,3-dimethyl-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-  
20 indol-2-one which was characterised by <sup>1</sup>H nmr and  
MS.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.4(6H s), 3.05 (1H broad),  
3.95(4H s), 6.96(1H d), 7.04(1H t), 7.12(2H m).

25

MS shows 206 (MH<sup>+</sup>) base peak.

- (11) 1-(2-Hydroxy-1-ethyl)-3-methyl-3-methylthio-1,3-dihydro-2H-indol-2-one: Prepared from 3-methyl-3-methylthioindol-2(3H)-one and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described for  
5 3,3-dimethyl-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one.

MS shows 238 (MH<sup>+</sup>) base peak.

- 10 (12) 3-Ethyl-1-(2-hydroxy-1-ethyl)-3-methyl-1,3-dihydro-2H-indol-2-one: Prepared from 3-ethyl-3-methylindol-2(3H)-one (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol. 4 page 657) and 2-(2-chloroethoxy)tetrahydro-2H-pyran  
15 as described in above.

MS shows 220 (MH<sup>+</sup>) base peak.

- (13) 5-Bromo-3,3-dimethyl-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one : Prepared from 5-bromo-3,3-dimethyl-1,3-dihydro-2H-indol-2-one and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described  
20 above.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39 (6H s), 3.05 (1H broad),  
25 3.95 (4H s), 6.8 (1H d), 7.3 (2H m),



- (14) 1-(2-Hydroxy-1-ethyl)-3,3,5-trimethyl-1,3-dihydro-2H-indol-2-one : Prepared from 3,3,5-trimethyl-1,3-dihydro-2H-indol-2-one (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol. 4 page 657) and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described above.  
MS shows 220 (MH<sup>+</sup>) base peak and 237 (M+NH<sub>4</sub>)
- (15) 5-Chloro-3,3-dimethyl-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one : Prepared from 5-chloro-3,3-dimethyl-1,3-dihydro-2H-indol-2-one (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol.4, page 657) and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described above.  
  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ1.39 (6H s), 3.05 (1H broad), 3.95(4H s), 6.8 (1H d), 7.3 (2H m),
- (16) 1-(2-Hydroxy-1-ethyl)-3,3,7-trimethyl-1,3-dihydro-2H-indol-2-one : Prepared from 3,3,7-trimethyl-1,3-dihydro-2H-indol-2-one (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol. 4 page 657) .and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described above.  
MS shows 220 (MH<sup>+</sup>) base peak and 237 (M+NH<sub>4</sub>)

- (17) 3,3-Dimethyl-1-(2-hydroxy-1-ethyl)-5-methoxy-1,3-dihydro-2H-indol-2-one: Prepared from 3,3-dimethyl-5-methoxy-1,3-dihydro-2H-indol-2-one (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol. 4 page 657) and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described above.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39 (6H s), 3.05 (1H broad), 3.82 (3H s), 3.95 (4H s), 6.8 (1H d), 7.3 (2H m),

- (18) 1-(2-Hydroxy-1-ethyl)-3,3,4-trimethyl-1,3-dihydro-2H-indol-2-one : Prepared from 3,3,4-trimethyl-1,3-dihydro-2H-indol-2-one (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol.4, page 657) and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described above.

MS shows 220 (MH<sup>+</sup>) base peak and 237 (M+NH<sub>4</sub>)

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- (19) 1-(2-Hydroxy-1-ethyl)-3,3,6-trimethyl-1,3-dihydro-2H-indol-2-one: Prepared from 3,3,6-trimethyloxindole (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol. 4 page 657) and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described above.

25

MS shows 220 ( $MH^+$ ) base peak and 237 ( $M+NH_4$ )

- (20) 1-(2-Hydroxy-1-ethyl)-3-spiro-1'-cyclopropyl-1,3-dihydro-2H-indol-2-one: Prepared from 3-spiro-1'-cyclopropyl-1,3-dihydro-2H-indol-2-one and 2-(2-chloroethoxy)tetrahydro-2H-pyran.

$^1H$  NMR ( $CDCl_3$ )  $\delta$  1.54 (2H m), 1.78 (2H m), 3.85 (4H m), 6.82 (1H d), 7.02 (2H m), 7.22 (1H m)

10

- (21) 1-(2-Hydroxy-1-ethyl)-3-spiro-1'-cyclopentyl-1,3-dihydro-2H-indol-2-one 60% Sodium Hydride in oil dispersion (0.132g, 3.29mmols) was added to 3-spiro-1'-cyclopentyl-1,3-dihydro-2H-indol-2-one (0.513g, 2.74mmols) dissolved in N-methylpyrrolidinone (5ml) followed by chloroethyl tetrahydropyran (0.541g, 3.29mmols) and the resultant mixture heated to 80C for 12h. The mixture was cooled water (30ml) was added and the product extracted into ethyl acetate (2x75ml), dried ( $MgSO_4$ ), filtered and concentrated in vacuo to give an oil. To this residue was added methanol (20mls) and para-toluenesulfonic acid (0.08g) and the mixture stirred at ambient temperature for 16h. The solvent was evaporated in vacuo and the resulting oil was purified by column chromatography

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on silica with ethyl acetate/ hexane to give an oil.

- 5 (22) 5-Fluoro-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one (2.4g, 15.9mmol) (prepared according to the method of Clark et al., Synthesis (1991) 871) was dissolved in freshly distilled tetrahydrofuran with tetramethylethylenediamine (3.7g, 31.9mmol) and was  
10 cooled to  $-75^{\circ}\text{C}$ . under nitrogen. n-Butyllithium (2.4 equivalents) was added and the mixture was stirred at  $-75^{\circ}\text{C}$ . for 40 minutes. Iodomethane (9g, 63mmol) was added and the mixture was allowed  
15 to warm to room temperature. After two hours' stirring at this temperature, water (5 ml) was added and the mixture was concentrated under reduced pressure, the resulting oil was taken up in  
20 dichloromethane, washed with dilute hydrochloric acid, dried ( $\text{MgSO}_4$ ), filtered and concentrated to dry under reduced pressure to give a yellow oil. This oil was dissolved in N-methylpyrrolidone and  
stirred at room temperature under nitrogen. Sodium hydride (0.625g, 15.6mmol) was added and the  
25 mixture was stirred until gas evolution ceased. 2-(2-Chloroethoxy)tetrahydro-2H-pyran (2.5g, 15mmol) and sodium iodide (0.1g, 0.66mmol) was added and the mixture was warmed to  $75^{\circ}\text{C}$ . for 15 hours.

Water was added and the mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate, washed (x3) with water, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting oil was taken up in methanol, para toluenesulphonic acid (0.1g, 0.5mmol) was added and the mixture was stirred at room temperature for 12h. The mixture was concentrated under reduced pressure, taken up in ethyl acetate, washed (x 3) with aqueous sodium hydrogen carbonate solution dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel, (eluent hexane/ethyl acetate) to give 5-fluoro-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one as a yellow oil. MS shows 224 (MH<sup>+</sup>) base peak and 241 (M+NH<sub>4</sub>)

(23) 5,6-Difluoro-3,3-dimethyl-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one: Prepared from 5,6-difluoro-1,3-dihydro-2H-indol-2-one and converted to 5,6-difluoro-3,3-dimethyl-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one as described for the synthesis of 3,3-dimethyl-5-fluoro-1-(2-hydroxy-1-ethyl)-1,3-dihydro-2H-indol-2-one.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.38 (6H s), 3.20 (1H broad),  
3.84 (4H m), 6.7 (1H dd), 7.03 (1H dd)

- (24) 1-(2-Chloroethyl)-1,3-dihydro-2H-indol-2-one : 1-  
5 (2-Chloroethyl)-1H-indole-2,3-dione [C.A. Reg no.  
77218-99-6] was suspended in acetic acid and  
hydrogenated at 60 p.s.i., at room temperature, in  
the presence of 70% perchloric acid and 5%  
palladium on charcoal for 24h. The clear solution  
10 was filtered and concentrated under reduced  
pressure. The residue was purified by  
chromatography on silica gel, eluent chloroform, to  
give 1-(2-chloroethyl)-1,3-dihydro-2H-indol-2-one  
as a white solid, melting point  $74^\circ\text{C}$ .  
15
- (25) 1-(2-Chloro-1-ethyl)-5-fluoro-1H-indole-2,3-dione :  
5-Fluoro-1H-indole-2,3-dione was dissolved in  
dimethylformamide. Sodium hydride (60% dispersion  
in mineral oil) (1.2 equivalents) was added in  
20 portions with stirring and cooling (ice-water bath)  
and the mixture was stirred until gas evolution  
ceased. 1-Bromo-2-chloroethane (1.2 equivalents)  
was added dropwise. The mixture was stirred at  
room temperature for 24 hours and then quenched  
25 into water and extracted into chloroform. The  
combined organic phases were washed with water,  
dried ( $\text{MgSO}_4$ ), filtered and concentrated under

reduced pressure. The resulting oil was purified by chromatography on silica gel, eluent chloroform, to give 1-(2-chloro-1-ethyl)-5-fluoro-1H-indole-2,3-dione as a red solid.

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Melting point 103° C.

(26) 1-(2-Chloro-1-ethyl)-1,3-dihydro-5-fluoro-2-oxo-2H-indole-3-spiro-2'-1,3 dithiane

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A solution of 1-(2-chloro-1-ethyl)-5-fluoro-1H-indole-2,3-dione, propanedithiol (1.2 equivalents) in chloroform was added dropwise to a stirred solution of boron trifluoride etherate in acetic acid and chloroform which was maintained at a gentle reflux throughout the addition. After 6 hours' reaction the mixture was cooled, washed with water and sodium hydrogen carbonate solution, dried (MgSO<sub>4</sub>) and filtered through a pad of flash silica using chloroform as eluent. The combined fractions were evaporated under reduced pressure to give 1-(2-chloro-1-ethyl)-1,3-dihydro-5-fluoro-2-oxo-2H-indole-3-spiro-2'-1,3 dithiane.

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Melting point 122° C.

- (27) 1-(2-Chloro-1-ethyl)-5-fluoro-1,3-dihydro-2H-indole-2-one: 1-(2-chloro-1-ethyl)-1,3-dihydro-5-fluoro-2-oxo-2H-indole-3-spiro-2'-1,3 dithiane was dissolved in a mixture of ethanol/tetrahydrofuran (3:2). Raney nickel was added and the mixture was heated under reflux with vigorous stirring for 3h. The cooled solution was filtered, evaporated under reduced pressure and triturated with ether to give 1-(2-chloro-1-ethyl)-5-fluoro-1,3-dihydro-2H-indole-2-one as a white solid, melting point 127° C.
- (28) 1-(2-Chloro-1-ethyl)-3,3-difluoro-1,3-dihydro-2H-indole-2-one :1-(2-Chloro-1-ethyl)-1H-indole-2,3-dione (1.1g, 5.2mmol) [C.A. Reg no. 77218-99-6] was heated to 65°C. under nitrogen in diethylaminosulfur trifluoride (3ml). The reaction mixture was poured onto water and extracted with chloroform. The organic phase was washed with sodium hydrogen carbonate solution, dried (MgSO<sub>4</sub>) and filtered to give 1-(2-chloro-1-ethyl)-3,3-difluoro-1,3-dihydro-2H-indole-2-one as a dark oil. MS shows 231 and 233 (MH<sup>+</sup>)
- (29) 1-(2-Chloro-1-ethyl)-3,3,5-triifluoro-1,3-dihydro-2H-indole-2-one: Prepared from 1-(2-chloroethyl)-5-



fluoro-1H-indole-2,3-dione and diethylaminosulfur trifluoride.

MS shows 249 and 251 (MH<sup>+</sup>)

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(30) 1-(2-Chloro-1-ethyl)-3-spiro-1'-cyclohexyl-1,3-dihydro-2H-indol-2-one 60% Sodium hydride in oil dispersion (0.46g, 11.46mmols) added was added to 3-spiro-1'-cyclohexyl-1,3-dihydro-2H-indol-2-one (1.922g, 9.55mmols) dissolved in dimethylformamide (25mls) followed by bromochloroethane (1.643g, 11.46mmols) and the resultant mixture stirred for 2 hours at ambient temperature. Water (30mls) was added and the product extracted into ethyl acetate (2x75ml) the ethyl acetate layer dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. The resulting oil purified by column chromatography on silica with ethyl acetate / hexane to give an oil).

20 (31) 3,3-Dimethyl-1-(2-methanesulfonyloxy-1-ethyl)-1,3-dihydro-2H-indol-2-one  
Sodium hydride (60% oil dispersion, 2.98g, 74.4 mmol) was washed with hexane, the hexane decanted and replaced with dimethylformamide (30ml). To this mixture was added dropwise during 30mins with stirring under nitrogen at ambient temperature 3,3-dimethyl-1,3-dihydro-2H-indol-2-one (10g, 0.062mol)

in dimethylformamide (220ml). This mixture was stirred for 1h at ambient temperature then 2-(2-chloroethoxy)-2-tetrahydro-2H-pyran (12.25g) was added in one portion, The mixture was heated to 80C for 1.25h then poured into water (750ml) and extracted with ethyl acetate (3x200ml). The combined extracts were washed with water, dried (MgSO<sub>4</sub>), filtered, and the filtrate evaporated in vacuo to give an oil 24.6g, which was dissolved in methanol (50ml) and treated with para-toluenesulfonic monohydrate (1.6g, 8.4mmol) and stirred for 16h, at ambient temperature under nitrogen. The solvent was removed in vacuo and the residue dissolved in ethyl acetate and washed with aqueous potassium carbonate solution (2x), dried (MgSO<sub>4</sub>), filtered, and evaporated in vacuo to give an oil 15.1g which was dissolved in dichloromethane (75ml) and triethylamine (9.41g 93mmol) was added followed by dropwise addition of methanesulfonyl chloride (6.0ml, 77.5mmol) during 4 mins and then stirred for 1.25h. The solvent was then evaporated in vacuo and the residue partitioned between ethyl acetate and water, the organic extract washed with brine, dried (MgSO<sub>4</sub>), filtered, and the filtrate evaporated in vacuo to give an oil 18.8g. This oil was triturated with a small quantity of diethyl ether and the resultant cream coloured precipitate

isolated by filtration and dried in vacuo to give a solid 13.16g. Further purification was effected by trituration with warm diethyl ether to give a solid.

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(32) 1-(2-Methanesulfonyloxy-1-ethyl)-3-spiro-1'-cyclopentyl-1,3-dihydro-2H-indol-2-one:

Triethylamine (0.246g, 2.43mmols) was added to 1-(2-hydroxy-1-ethyl)-3-spiro-1'-cyclopentyl-1,3-dihydro-2H-indol-2-one (0.433g, 1.87mmols) dissolved in dichloromethane (10mls) followed by methanesulfonyl chloride (0.16mls 2.06mmols) and the mixture stirred at ambient temperature for 3 hours. Water was added (20mls) the dichloromethane layer separated and dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to give a solid.

10

(33) 1-Dimethylamino-2-(4-fluoro-2-nitro)phenylethene

A mixture of 4-fluoro-2-nitrotoluene (50g, 0.32mol), dimethylformamide dimethylacetal (76.77g) and dimethylformamide (910ml) were heated under reflux under nitrogen with stirring for 7h, cooled allowed to stand for 16h, poured into ice-water (2000ml), stirred for 15mins, the resultant precipitate isolated by filtration, washed with water (500ml), dried to give a red solid.

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(34) 6-Fluoroindole

A 40 litre Cook hydrogenator was charged under a nitrogen atmosphere with 10% palladium on charcoal (9g) suspended in toluene (400ml). To this  
5 suspension was added 1-dimethylamino-2-(4-fluoro-2-nitro)phenylethene (137.2g, 0.653mol) in toluene (1400ml) and the mixture hydrogenated at 80psifor 3.5h. The suspesnion was then filtered through a celite pad, which was washed through with toluene  
10 (2x200ml) and the filtrate and washings evaporated under reduced pressure to give a brown oil which crystallised on standing to a yellow brown solid 93.65g. This solid was dissolved in ethyl acetate-hexane (7:3) and filtered through a pad of flash  
15 silica. The required fractions were collected and evaporated under reduced pressure to giv a pale brown solid.

Similarly prepared was 6-Cyanoindole.

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(35) 7-Fluoroindole

2-Fluoronitrobenzene (20.0g, 0.142mols) dissolved in dry tetrahydrofuran (400mls) and cooled to -  
50degC. Vinylmagnesium chloride (288mls, 15%wt/vol)  
25 added at -45degC and stirred at this temperature for one hour. Poured onto saturated ammonium chloride (600mls). Separated and aqueous extracted

with diethyl ether (2x200mls). Dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to yield a dark oil which was purified column chromatography on silica using toluene as mobile phase. Fractions concentrated to yield a crystalline solid.

Similarly prepared was 6-Fluoro-7-methylindole.

(36) 7-Fluoroindole

To a stirred solution of boron trichloride in dichloromethane (1.0M, 3.650l, 3.65mol) at -10C under nitrogen was added 2-fluoroaniline (387g, 3.48mol) and the temperature rose to 18C. The mixture was stirred for 45 mins before chloroacetonitrile (300g, 3.97mol) followed by aluminium chloride (500g, 3.75mol). 1,2-Dichloroethane (5.7l) was added the mixture heated and the dichloromethane distilled from the reaction vessel. The dichloroethane solution was then heated at 78-80C for 18h. The reaction mixture was then cooled to 2C and hydrochloric acid (2.5M 450ml) was added slowly with a resultant exotherm. More hydrochloric acid (2.5M, 5.550l) was added and then the mixture was warmed to reflux for 10mins then cooled. The dichloroethane layer was separated and the aqueous layer extracted with dichloromethane (1l) combined with the dichloroethane, washed with

brine (2l), dried (MgSO<sub>4</sub>), filtered and the solvent evaporated in vacuo to give a solid 321.7g. This solid was dissolved in a mixture of dioxan (10l) and water (1l) and treated under nitrogen with sodium borohydride (73.0g, 1.93mol) then heated under reflux for 1h. More sodium borohydride (12g) was added and the mixture heated for a further 3h, cooled to 45C and the solvent removed in vacuo. The residue was partitioned between dichloromethane (2000ml) and water (2000ml). The organic layer was separated, dried (MgSO<sub>4</sub>), filtered and evaporated in vacuo to give an oil which was further purified by filtering through silica.

Similarly prepared was 6,7-Difluoroindole.

(37) 5,6-Difluoroindole Fuming nitric acid (25ml) was stirred with cooling (ice/water bath) and 3,4-difluorophenylacetonitrile (5g, 32.7mmol) was added dropwise. The mixture was left to stir for 15h and was then poured onto ice. The mixture was neutralised with sodium hydrogen carbonate and extracted with dichloromethane. The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to give 2(2'-nitro-4',5'-difluorophenyl)-acetonitrile as a yellow oil which was immediately in ethanol/acetic

acid (19:1) and hydrogenated over 10% palladium on charcoal at 65 p.s.i. The reaction mixture was filtered and concentrated under reduced pressure. The oily residue was taken up in ethyl acetate and washed with aqueous sodium hydrogen carbonate solution. The combined organic phases were dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure to give 5,6-Difluoroindole as a yellow solid. Mass spectroscopy showed 154.1 (MH<sup>+</sup>).

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(38) 4-(6-Fluoroindol-3-yl)-1,2,5,6-tetrahydropyridine

Powdered potassium hydroxide (144.4g) was added carefully to a mechanically stirred mixture of 6-fluoroindole (49.23g, 0.364mol) and piperidine monohydrate (111.93g, 0.728mol) in methanol (1500ml) The mixture was then heated under reflux under nitrogen for 18h and then more potassium hydroxide (40g) was added and the reaction mixture heated under reflux for a further 4h. The reaction mixture was allowed to cool to room temperature and poured onto ice-water (3000ml) and stirred for 1h and the precipitated solid isolated by filtration and dried at 50C in vacuo to give a solid.

25 (39) 4-(6-Fluoroindol-3-yl)piperidine

A mixture of platinum oxide (1.0g) in ethanol (37.5ml) and glacial acetic acid (12.5ml) was

treated under nitrogen with 4-(6-fluoroindol-3-yl)-  
1,2,5,6-tetrahydropyridine (20g, 92.6mmol) in  
ethanol (187.5ml) and glacial acetic acid (62.5ml).  
The nitrogen was evacuated and hydrogen was  
5 admitted. The reaction mixture was then  
hydrogenated at 60psi until the reaction was  
complete by tlc. The catalyst was removed by  
filtration and the solvent evaporated in vacuo to  
give a yellow solid which after drying at 60C in  
10 vacuo weighed.

EXAMPLE 1

3,3-Dimethyl-1-(2-[4-(7-fluoroindol-3-yl)-1,2,5,6-  
15 tetrahydro-1-pyridyl]-1-ethyl)-1,3-dihydro-2H-indol-2-  
one  
4-(7-Fluoroindol-3-yl)-1,2,5,6-tetrahydropyridine  
(2.0g, 9.26mmols), 3,3-dimethyl-1-(2-methanesulfonyloxy-  
1-ethyl)-1,3-dihydro-2H-indol-2-one (2.623g, 9.26mmols),  
20 sodium carbonate (2.947g, 27.8mmols), water (20mls)  
combined and heated to 90degC for 3 hours. Extracted  
into ethyl acetate (2x50ml). Dried (MgSO<sub>4</sub>), filtered and  
concentrated in vacuo. The resultant solid was  
recrystallised from ethyl acetate and then converted to  
25 the hydrochloride salt (0.85g).m.p 235-236 degC



EXAMPLE 2

3,3-Dimethyl-1-(2-[4-(6-fluoro-7-methylindol-3-yl)-  
1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl)-1,3-dihydro-2H-  
5 indol-2-one hydrochloride.

3,3-dimethyl-1-(2-methanesulfonyloxy-1-ethyl)-1,3-  
dihydro-2H-indol-2-one (6.21g, 0.0219mols) and 4-(6-  
fluoro-7-methylindol-3-yl)-1,2,5,6-tetrahydropyridine  
10 (5.05g, 0.0219mols) were dissolved in dry acetonitrile  
(220 mL). To this potassium carbonate (3.5g, 0.026mol)  
and potassium iodide (4.23g, 0.026 mol) were added. The  
mixture was stirred, whilst heating under reflux, for  
4h. The hot mixture was filtered off from inorganic  
15 material after this time and the filtrate was evaporated  
to dryness *in vacuo*. The residue was dissolved in  
chloroform, to which a minimum of methanol was added to  
aid solubility and filtered off from any remaining  
inorganic materials. This filtrate was column  
20 chromatographed using initially chloroform with "flash"  
silica gel as the stationary phase. The bulk of the  
material was eluted using 2% methanol in chloroform, any  
remaining material was removed with 5% methanol in  
chloroform.

25

The fractions containing product were bulked and  
evaporated to dryness, *in vacuo*, the residue was

trituated with ethyl acetate, filtered off and dried in a vacuum oven at 60°C. The weight of freebase = 6.81g, melting point = 219°C. This material (1g) was dissolved in boiling ethyl acetate (100mL) and enough ethanolic  
5 hydrogen chloride was added to this solution to render it acid when tested with pH paper. The solution was chilled and a hydrochloride salt crystallised out. The salt was filtered off, washed with ethyl acetate, ether, and dried, melting point = 228.8-233.3°C.

10

EXAMPLE 3

3,3-Dimethyl-1-(2-[4-(7-fluoroindol-3-yl)-1-piperidinyl]-1-ethyl)-1,3-dihydro-2H-indol-2-one

15 Monohydrochloride

3,3-Dimethyl-1-(2-[4-(7-fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl)-1,3-dihydro-2H-indol-2-one (0.6g, 1.36mmol) dissolved in ethanol (40mls) and acetic acid (4mls) was added to 10% platinum oxide/  
20 charcoal. Hydrogen was admitted for 12h at 60psi the catalyst was then removed by filtration, the catalyst washed with ethanol (3x75mls), concentrated in vacuo and the resulting oil purified by column chromatography on silica with ethyl acetate/ Hexane. The fractions  
25 containing product were collected and the solvent evaporated in vacuo to give a solid which was converted

to the hydrochloride, which was subsequently dried in vacuo to give a solid, mp 172-174°C

5 EXAMPLE 4

3,3-Dimethyl-1-{2-[4-(6-fluoroindol-3-yl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2H-indol-2-thione Monohydrochloride

10 Phosphorus pentasulfide (0.164g) was added to 3,3-dimethyl-1-{2-[4-(6-fluoroindol-3-yl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2H-indol-2-one (0.5g, 1.23mmol) dissolved in pyridine (15mls) and the mixture heated under reflux for 12 hours. The resultant mixture  
15 concentrated in vacuo and dissolved in ethyl acetate (50mls) and washed with water (50ml). The ethyl acetate layer dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to give a solid which was purified by column chromatography using silica / dichloromethane then ethyl  
20 acetate. The fractions containing product were concentrated and converted to the hydrochloride salt, mp 227-229°C.

Similarly prepared were:

25

3,3-Dimethyl-N,N-dimethyl-1-{2-[4-(6-fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-1,3-dihydro-2H-2-oxo-indole-5-carboxamide hydrochloride. mp = 210.2-215°C

- 5 1-{2-[4-(6-Chloroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-3,3-dimethyl-N,N-dimethyl-1,3-dihydro-2H-2-oxo-indole-5-carboxamide. mp = 225°C

- 3,3-Dimethyl-1-{2-[4-(7-chloroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 248.9-249.9°C
- 10

- 3,3-Dimethyl-1-{2-[4-(6-fluoro-7-methylindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 228.8-233.3°C
- 15

- 1-{2-[4-(6,7-Difluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-3,3-dimethyl-5-fluoro-1,3-dihydro-2H-indol-2-one hydrochloride. mp >250°C
- 20

3,3-Dimethyl-5,6-difluoro-1-{2-[4-(6-fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 227-229°C

- 25 1-{2-[4-(6-Fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-3-methyl-3-methylthio-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 165-168°C

1-(2-[4-(6-Fluoroindol-3-yl)-1-piperidinyl]-1-ethyl)-  
3,3,5-trimethyl-1,3-dihydro-2H-indol-2-one  
hydrochloride. mp = 220-222°C

5

5,6-Difluoro-3,3-dimethyl-1-(2-[4-(6-fluoroindol-3-yl)-  
1-piperidinyl]-1-ethyl)-1,3-dihydro-2H-indol-2-one  
hydrochloride. mp = 231-233°C

10 3,3-Dimethyl-1-(2-[4-(6-fluoro-1-methylindol-3-yl)-1-  
piperidinyl]-1-ethyl)-5-methoxy-1,3-dihydro-2H-indol-2-  
one hydrochloride. mp = 252-255°C

3-Ethyl-1-(2-[4-(6-fluoroindol-3-yl)-1-piperidinyl]-1-  
15 ethyl)-3-methyl-1,3-dihydro-2H-indol-2-one  
hydrochloride. mp = 221-223°C

3,3-Dimethyl-5-fluoro-1-(2-[4-(6-fluoro-1-methylindol-3-  
yl)-1-piperidinyl]-1-ethyl)-1,3-dihydro-2H-indol-2-one  
20 hydrochloride. mp >260°C

1-(2-[4-(5,6-Difluoroindol-3-yl)-1-piperidinyl]-1-  
ethyl)-3,3-dimethyl-1,3-dihydro-2H-indol-2-one  
hydrochloride. mp >260°C

25

3-Ethyl-1-{2-[4-(6-fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-3-methyl-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 196-204°C

- 5 1-{2-[4-(6-Fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-3,3,5-trimethyl-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 206-222°C

- 3,3-Dimethyl-5-fluoro-1-{2-[4-(7-fluoroindol-3-yl)-1-piperidinyl]-1-ethyl}-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 198-200°C
- 10

- 5-Chloro-3,3-dimethyl-1-{2-[4-(6-fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 233.9-236.2°C
- 15

- 1-{2-[4-(6,7-Dichloroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-3,3-dimethyl-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 262-266°C
- 20

1-{2-[4-(5,7-Difluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-1,3-dihydro-3-spiro-4'-(1'-methylpiperidino)-2H-indol-2-one. mp = 210-212°C

- 25 3,3-Dimethyl-1-{2-[4-(5-fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl}-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 230°C

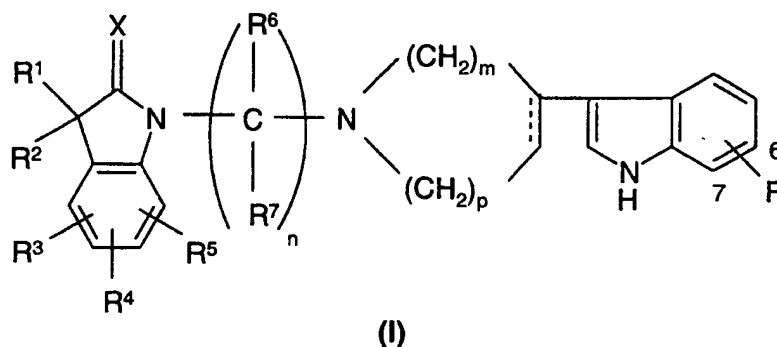
3,3-Dimethyl-1-(2-[4-(4-fluoroindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl)-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 235.6-236.6°C

5

3,3-Dimethyl-1-(2-[4-(5-fluoro-1-methylindol-3-yl)-1,2,5,6-tetrahydro-1-pyridyl]-1-ethyl)-1,3-dihydro-2H-indol-2-one hydrochloride. mp = 194-197°C

CLAIMS

1. A compound of the formula:



5

in which n is 1 to 6, m is 1 or 2 and p is 1 or 2,

R<sup>1</sup> and R<sup>2</sup> are each hydrogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, HO-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkylthio, halo, optionally substituted phenyl, optionally substituted phenyl-C<sub>1-4</sub> alkyl, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are attached form a C<sub>3-6</sub> cycloalkyl group, >C=O, C=NOR' where R' is hydrogen or C<sub>1-4</sub> alkyl,

15

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are each hydrogen, halo, nitro, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl-CO-, where m is 0, 1 or 2, R'R''N-SO<sub>2</sub>-, -COOR', -CONR'R'', -NR'R'', -N(OR')COOR'', -COR', -NHSO<sub>2</sub>R', where R' and R'' are each hydrogen or C<sub>1-4</sub> alkyl,

20



R<sup>6</sup> and R<sup>7</sup> are each hydrogen or C<sub>1-4</sub> alkyl,

X is oxygen or sulphur,

5

the dotted line represents an optional double bond,  
and

10

the fluorine atom is attached at the 6- or  
7-position;

and salts thereof.

2. A compound according to Claim 1 in which the  
15 fluorine substituent is in the 6-position, and X is  
oxygen.

3. A compound according to either of Claims 1 or 2 in  
which the dotted line represents a double bond.

20

4. A compound according to any of the preceding claims  
in which m is 2 and p is 1.

5. A compound according to any of the preceding claims  
25 in which R<sup>1</sup> and R<sup>2</sup> are each hydrogen, C<sub>1-4</sub> alkyl or  
C<sub>1-4</sub> alkylthio.

6. A compound according to any of Claims 1 to 4 in which  $R^1$  and  $R^2$  are both  $C_{1-4}$  alkyl or benzyl.
- 5 7. A compound in which n is 2 and  $R^6$  and  $R^7$  are hydrogen.
8. A pharmaceutical formulation comprising a compound according to any of Claims 1 to 8 associated with a  
10 pharmaceutically acceptable diluent or carrier therefor.
9. A compound according to any of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use  
15 as a pharmaceutical.
10. The use of a compound according to any of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for  
20 treating a disorder of the central nervous system.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01474

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/14 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 675 801 A (RHONE-POULENC RORER S.A.) 30 October 1992 (1992-10-30) page 7, line 18 - line 23; claims ---	1,8,10
A	EP 0 780 388 A (LILLY INDUSTRIES LTD.) 25 June 1997 (1997-06-25) cited in the application page 7, line 24 - line 29; claims -----	1,8,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

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Information on patent family members

International Application No

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